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ORIGINAL ARTICLE

Cognitive impairment in type 2 diabetes mellitus

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KEYWORDS

P300;
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Abstract *Background:* Type 2 diabetes mellitus (T2DM) is a modern day epidemic. Chronic course of diabetes is detrimental to the cognitive functions.

Aim: To decipher the pattern of cognitive impairment in relation to the duration of diabetes.

Study design: Cross-sectional.

Material and methods: T2DM patients (Group I: ≤ 5 years duration of diabetes, $n = 11$; Group II: > 5 years duration of diabetes, $n = 17$) without clinical evidence of central nervous system damage and non-diabetic controls ($n = 18$) were studied clinically and P300 event-related potentials (ERPs) recorded using three stimuli oddball paradigm. Subjects were examined with Folstein mini-mental state examination (MMSE) for cognitive function and those showing scores more than 26 (maximum score = 30) were enrolled for the study. Patients with known diabetic complications were excluded.

Results: P300 latencies in diabetic group did not relate linearly to the duration of diabetes. Diabetic subgroups with ≤ 5 years and > 5 years duration of diabetes showed striking differences, patients with over 5 years of disease duration had much prolonged P300 latencies in contrast to patients with 5 years or less disease duration who showed trends similar to that of control group. Differences in P300 amplitudes between groups were non-significant. Hypertensive diabetics showed much prolongation in P300 latencies compared to normotensive diabetics.

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Conclusions: P300 ERPs revealed cognitive dysfunction which was not detected by neuro-psychometric test (MMSE). Patients with T2DM have decreased cognitive function which is more prominent when the disease duration exceeds 5 years. Co-existence of hypertension with T2DM further increases the risk of cognitive impairment.

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1. Introduction

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide, and has become a significant public health problem [1]. It is associated with mortality and significant morbidity, including neurological disability. Although the effects of diabetes on the peripheral nervous system (PNS) are well established, its effects on higher mental functions (HMF) are often overlooked, due to lack of clear signs and unavailability of standard assessment techniques [2,3]. Even mild form of cognitive dysfunction might hamper everyday activities depending on the work and situation, which requires various cognitive domains such as general intelligence, processing speed, psychomotor efficiency, attention, perception, learning, memory, and executive functions [4]. Several studies have reported a cognitive decline in T2DM [5,6]. However, there is no consensus as to the specific domains of cognition that may be affected by T2DM, and thus, which domains can be recommended for testing.

P300 event-related potential (ERP) measures the speed of neural events related to attention and short-term memory. Hence, P300 latency increases systematically as cognitive capability decreases [7]. P300, having a high temporal resolution, demonstrates reasonable success as a potential tool to assess the decline in cognitive functions when compared to functional imaging (Positron Emission Tomography – PET, functional Magnetic Resonance Imaging – fMRI) which possess good spatial resolution [8,9].

The objective of the present study is to decipher the pattern of cognitive impairment in relation to the duration of diabetes, using P300 ERP, three stimuli odd-ball paradigm.

2. Material and methods

2.1. Subjects

A cross-sectional study was conducted after approval by the Institutional Ethics Committee and obtaining written consent from all subjects. The study group comprised of twenty eight T2DM subjects belonging to both genders in the age group 40–65 years. The study group was divided into two sub-groups (Group I: ≤ 5 years duration of diabetes, $n = 11$; Group II: > 5 years duration of diabetes, $n = 17$). Eighteen non-diabetic individuals, matched by age, were taken as the control group. The demographic and clinical data of the participants are listed in Table 1. Patients with known diabetic complications such as retinopathy, nephropathy, and peripheral neuropathy were excluded from the study. Persons with a history of auditory disorders and psychological disturbances, which might interfere with auditory P300 assessment, were also excluded.

2.2. Plasma glucose

Plasma glucose levels were assessed through use of the glucose oxidase method. Fasting plasma glucose level of ≤ 110 mg/dL

without history of diabetes mellitus was the inclusion criteria for controls.

2.3. Blood pressure (BP)

A sphygmomanometer was used to measure arterial blood pressure. BP was recorded on the left arm of the subjects in sitting posture. Systolic BP of ≤ 140 mm Hg and diastolic BP of ≤ 90 mm Hg without the history of hypertension were labeled as normotensives.

2.4. Mini-mental state examination (MMSE)

Subjects were examined through a Folstein mini-mental state examination (MMSE), a brief 30-point neuro-psychometric test, for cognitive functions which reflects orientation, memory, attention, ability to follow verbal and written commands, writing, and copying [10]. Subjects showing a score of higher than 26 (maximum score = 30), indicating no cognitive impairment, were selected for the study.

2.5. P300 potential

Nicolet Viking Select [Viasys Healthcare, USA] was used to elicit P300 cognitive potential. The investigation was performed in a silent room, with subjects in a reclining position with eyes closed, in order to eliminate disturbance caused by movement. Two channel recording was undertaken, active electrodes were connected to bilateral mastoids (A1/A2) and the reference electrodes were connected to the scalp at Cz and Pz position. The ground was connected to the Fpz location and impedance was kept below 5 kilo-ohms. Stimuli were delivered using TDH-39P headphones at a frequency of 1.0 Hz. A novel three stimuli odd-ball paradigm, characterized by random presentation of two rare (target) stimuli interspersed in presentation of frequent stimulus, was designed. The characteristics of the stimuli are depicted in Table 2. Against the background sounds of frequent and 1st rare stimuli, omitted sound served as 2nd rare stimulus. Subjects were asked to recognize and keep a mental count of both rare stimuli and not responding to frequent stimulus. The test was run for two sets to ensure the reproducibility of signals and the responses averaged over 200 sweeps in each set, in such a way that at least 40 artifact free ERPs for each rare stimulus is obtained, which is sufficient to stabilize P300 latency and amplitude.

2.6. Statistical analyses

Analyses of variance (ANOVA) and correlation statistics of peak latencies and peak amplitudes of P300 waves were performed using SPSS 13.0 and Origin Pro 8.0 software. p -value < 0.05 was considered as statistically significant.

Table 1 Demographic and clinical data of the participants.

Parameters	Non-diabetic controls (<i>n</i> = 18)	Diabetics	
		Group I ≤ 5 years (<i>n</i> = 11)	Group II > 5 years (<i>n</i> = 17)
Age(years)	50 \pm 7	52 \pm 6	53 \pm 6
Male gender (%)	44	63	58
Duration of diabetes (years)	–	3 \pm 2	10 \pm 4
Fasting plasma glucose (mg/dL)	98 \pm 8	159 \pm 59	152 \pm 48
<i>Anti-diabetic medication</i>			
Oral hypoglycemic agents (OHA) (%)	–	91	70
Insulins (%)	–	0	24
Combined OHA and insulins (%)	–	9	6
Hypertension (%)	38	63	82
Smoking (%)	38	18	29
Alcohol consumption (%)	22	36	29
Body mass index (BMI) (kg/m ²)	26.6 \pm 5.2	29.5 \pm 5.9	30.3 \pm 6.1
Mini-mental state examination (MMSE) score	28.4 \pm 1.4	28.3 \pm 1.1	27.9 \pm 0.8
P300 latency after 1st rare stimulus at Cz (ms)	313 \pm 19	311 \pm 23	334 \pm 31
P300 latency after 1st rare stimulus at Pz (ms)	309 \pm 21	322 \pm 36	343 \pm 30
P300 latency after 2nd rare stimulus at Cz (ms)	346 \pm 28	347 \pm 36	384 \pm 29
P300 latency after 2nd rare stimulus at Pz (ms)	352 \pm 29	375 \pm 29	395 \pm 34
P300 amplitude after 1st rare stimulus at Cz (μ V)	6.66 \pm 2.40	6.49 \pm 2.46	5.63 \pm 2.40
P300 amplitude after 1st rare stimulus at Pz (μ V)	5.45 \pm 2.23	5.46 \pm 2.85	4.64 \pm 1.85
P300 amplitude after 2nd rare stimulus at Cz (μ V)	4.45 \pm 1.37	4.43 \pm 1.72	4.62 \pm 1.56
P300 amplitude after 2nd rare stimulus at Pz (μ V)	4.16 \pm 1.39	2.95 \pm 1.24	3.52 \pm 1.15

Numbers represent mean \pm standard deviation except those specified as (%) represents percentage of subjects.

Table 2 Stimulus parameters.

Stimulus	Probability (%)	Type	Ear	Character	Polarity	Intensity (dB)	Frequency (kHz)
Frequent	60	Auditory	Both	Click	Rarefaction	70	0.75
1st Rare	20	Auditory	Both	Pip	Rarefaction	94	2.0
2nd Rare	20	–	–	Omitted stimulus	–	–	–

3. Results

Regression analysis of P300 latencies with respect to duration of diabetes did not relate linearly ($R < 0.2$). Longer duration of diabetes is associated with much more prolonged P300 latencies (Table 1, Fig. 1). At Cz position, mean P300 latencies after 1st rare stimulus were prolonged by -2 ms (F (1,27) = 0.129, p = 0.72) and 21 ms (F (1,33) = 5.806, p = 0.02) whereas after 2nd rare stimulus latencies were prolonged by 1 ms (F (1,27) = 0.016, p = 0.90) and 38 ms (F (1,33) = 15.533, p < 0.001), respectively in Group I and Group II than in controls. Similarly, at Pz position, mean P300 latencies after 1st rare stimulus were prolonged by 13 ms (F (1,27) = 1.674, p = 0.20) and 34 ms (F (1,33) = 15.777, p < 0.001) whereas after 2nd rare stimulus latencies were prolonged by 23 ms (F (1,27) = 4.216,

p = 0.05) and 43 ms (F (1,33) = 15.836, p < 0.001), respectively in Group I and Group II than in controls.

P300 amplitudes did not correlate linearly to the duration of diabetes on regression analysis ($R < 0.1$) and no significant difference was observed in Group I and Group II, compared to controls (Table 1, Fig. 2).

We also observed much delayed P300 latencies in hypertensive diabetics, in contrast to normotensive diabetics (Table 3).

4. Discussion

The present study involved a novel three stimuli odd-ball paradigm with both the rare stimuli as targets, hence making the test more objective and reliable since the analysis and judgment of the characteristics of numerous stimuli require elaborate neural processing. The findings of the current study

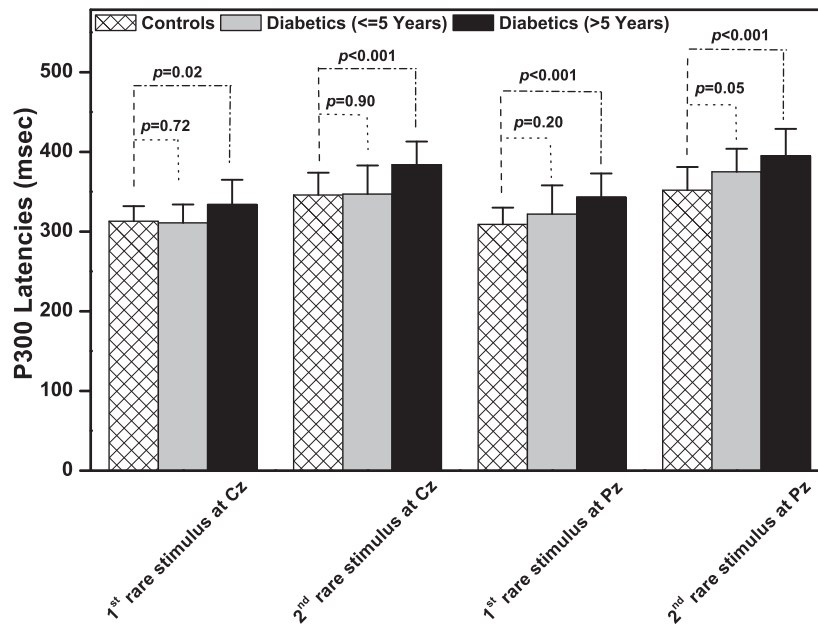


Figure 1 P300 latencies in Group I and Group II in comparison with controls.

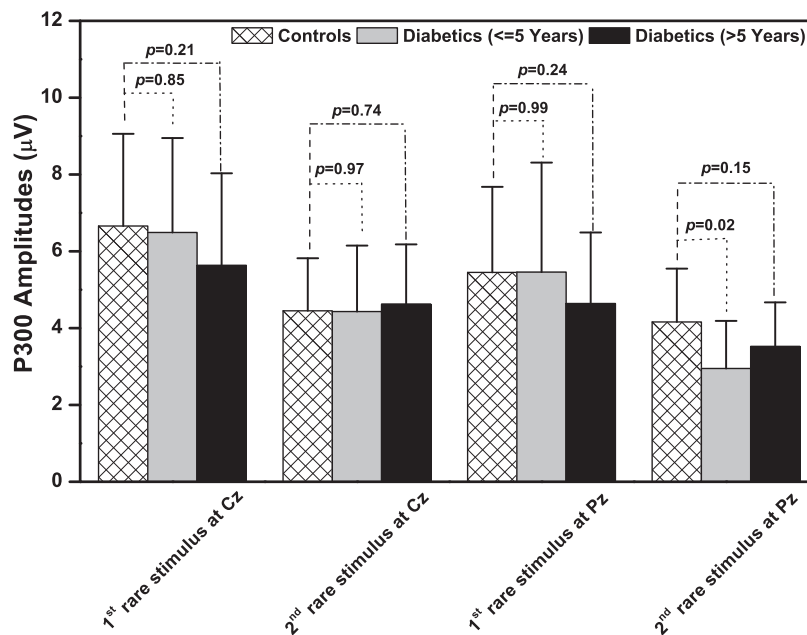


Figure 2 P300 amplitudes in Group I and Group II in comparison with controls.

strongly support the hypothesis that there is a relationship between cognitive dysfunction and duration of type 2 diabetes mellitus.

The present study demonstrates a more significant change in P300 latencies in diabetics than controls, which is in agreement with previous studies [11–14]. We could not find any linear correlation between P300 latencies and the duration of DM, which is consistent with the previous findings [15,16]. In our study, diabetics with ≤ 5 years of disease duration and those with > 5 years of disease duration showed significant difference in P300 latencies. This distinction in the sub-groups is probably brought about by the novelty of the test, which

increased the work load of the cognitive task by delivering stimuli at a higher rate, and making both rare stimuli as target stimuli. Since P300 latencies represent conduction time in neural circuitry involved in cognitive task [17], DM hampers the signal conduction in the neural network, which further deteriorates as the duration of disease increases.

Neither linear correlation between the P300 amplitudes and duration of diabetes was observed, nor any significant difference in Group I and Group II compared to controls. P300 amplitude is an index of brain processes elicited from tasks required in the maintenance of working memory [18]. P300 measures are affected by target stimulus probability such that low

Table 3 P300 parameters of normotensives and hypertensives in control and diabetic groups.

Parameters	Diabetics		Non-diabetic controls	
	Normotensives (n = 7)	Hypertensives (n = 21)	Normotensives (n = 11)	Hypertensives (n = 7)
P300 latency after 1st rare stimulus at Cz	315 ± 43	328 ± 25	314 ± 22	313 ± 15
P300 latency after 2nd rare stimulus at Cz	357 ± 37	373 ± 36	345 ± 26	347 ± 33
P300 latency after 1st rare stimulus at Pz	322 ± 40	339 ± 31	307 ± 24	311 ± 17
P300 latency after 2nd rare stimulus at Pz	382 ± 38	389 ± 32	353 ± 30	352 ± 30
P300 amplitude after 1st rare stimulus at Cz	6.27 ± 2.31	5.87 ± 2.50	6.90 ± 2.83	6.29 ± 1.62
P300 amplitude after 2nd rare stimulus at Cz	3.94 ± 1.36	4.74 ± 1.64	4.72 ± 1.52	4.03 ± 1.04
P300 amplitude after 1st rare stimulus at Pz	5.71 ± 2.53	4.71 ± 2.20	5.51 ± 1.94	5.37 ± 2.79
P300 amplitude after 2nd rare stimulus at Pz	2.72 ± 0.92	3.49 ± 1.24	4.46 ± 1.30	3.68 ± 1.50

Numbers represent mean ± standard deviation.

probability elicits larger P300 amplitudes because the immediate memory for the preceding target stimulus has decayed and is refurbished by the neural processing that occurs upon presentation of new target stimulus [19,20]. P300 amplitudes are also dependent on inter-stimulus interval (ISI) such that shorter ISIs have smaller amplitudes than those obtained with longer ISIs [21,22]. As our study involved higher stimulus frequency, which decreased the ISI and increased target stimulus probability, we obtained smaller P300 amplitudes in all participants, as compared to larger amplitudes in earlier studies [19,23].

Our findings suggest that DM duration is important in the pathogenesis of cognitive impairment. It is possible that metabolic imbalances and other factors could interact, either directly or indirectly and result in an altered central nervous system function and impaired cognition [24]. Long duration of DM being an atherogenic factor, it may increase the risk of cognitive dysfunctioning through well recognized associations with stroke, causing cerebral macrovascular disease and cerebral infarctions [25]. Chronic hyperglycemia is one of the determinants of cognitive decline in people with T2DM. The deleterious effects of hyperglycemia are mediated through an increased influx of glucose through the polyol pathway forming sorbitol and fructose, oxidative stress, and non-enzymatic glycation of biomolecules resulting in advanced glycation end products (AGE) [26].

Other likely mechanisms of cognitive dysfunction in T2DM are extensive leukoaraiosis (White matter hyperintense lesions – WMHLs) [27], atrophy in the region of hippocampus and amygdala [28] and insulin resistance. Insulin resistance contributes through the indirect mechanism of up-regulating hypothalamic–pituitary–adrenal axis, thereby causing hypercortisolemia related cognitive dysfunction [29].

Hypertension usually exists as a co-morbid condition with DM and may be a part of a larger metabolic syndrome, including hyperglycemia, hyperinsulinemia, and dyslipidemia. Hypertension and diabetes, when combined, increase the risk of cognitive impairment [30,31]. Our study also revealed a higher association of hypertension with diabetic group than control group, and there was significant difference in P300 trends with co-existence of DM and hypertension than DM alone.

Although several mechanisms may interact in order for diabetes and hypertension to cause cognitive impairment, hypertension causes cognitive decline through the vascular consequences of blood pressure load on the cerebral circula-

tion, both on large and small vessels. Large vessel disease mainly occurs through increased atherosclerosis and arterial stiffness, whereas small vessel disease is sustained by vascular remodeling, endothelial dysfunction, and the impairment of cerebral blood flow auto-regulation with increased susceptibility to hypo-perfusion. All these cause discrete brain lesions such as ischemic or hemorrhagic stroke, with the loss of brain tissue and cognitive deterioration [32].

5. Limitations

There are some limitations to our study. One limitation is the small sample size. Also unknown and sub-clinical complications, which are unaccounted for, may have a bearing on cognitive function.

6. Conclusions

P300 ERPs were able to reveal cognitive changes not detected by neuro-psychometric test (MMSE). Thus, P300 may be helpful in early detection of cognitive decline in DM and in identifying diabetic patients with potential pre-senile dementia. Moreover, cognitive dysfunction is not linearly related to the duration of diabetes. However, the decline is more prominent when the duration of DM is more than 5 years. The co-existence of hypertension with T2DM further increases the risk of cognitive impairment.

7. Conflict of interest

None.

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References

- [1] Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414(6865):782–7.
- [2] Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology* 2004;63(6):996–1001.
- [3] Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MMB. Association of diabetes mellitus and dementia: the Rotterdam study. *Diabetologia* 1996;39(11):1392–7.
- [4] Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 2008;29(4):494–511.
- [5] Richardson JTE. Cognitive function in diabetes mellitus. *Neurosci Biobehav Rev* 1990;14(4):385–8.
- [6] Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW, Gispen WH. Cerebral function in diabetes mellitus. *Diabetologia* 1994;37(7):643–50.
- [7] Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation, and findings. *Int J Psychophysiol* 2000;38(1):3–19.
- [8] Ohyama M, Senda M, Kitamura S, Terashi A. Changes in regional cerebral blood flow during auditory cognitive tasks—a PET activation study with odd-ball paradigm. *Rinsho Shinkeigaku* 1993;33(2):134–40.
- [9] Shaw NA. The temporal relationship between the brainstem and primary cortical auditory evoked potentials. *Prog Neurobiol* 1995;47(2):95–103.
- [10] Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189–98.
- [11] Mochizuki Y, Oishi M, Hayakawa Y, Matsuzaki M, Takasu T. Improvement of P300 latency by treatment in non-insulin-dependent diabetes mellitus. *Clin Electroencephalogr* 1998;29(4):194–6.
- [12] Chen X, Chen W, Chen SR, Luo YP. Event-related potentials P300 in type 2 diabetes mellitus. *Di Yi Jun Yi Da Xue Xue Bao* 2003;23(3):257–9.
- [13] Alvarenga KdeF, Duarte JL, da Silva DPC, Agostinho-Pesse RS, Negrato CA, Costa OA. Cognitive P300 potential in subjects with diabetes mellitus. *Rev Bras Otorrinolaringol* 2005;71(2):202–7.
- [14] Cooray G, Nilsson E, Wahlin A, Laukka EJ, Brismar K, Brismar T. Effects of intensified metabolic control on CNS function in type 2 diabetes. *Psych Endocrinol* 2011;36(1):77–86.
- [15] Dey J, Misra A, Desai NG, Mahapatra AK, Padma MV. Cognitive function in younger type II diabetes. *Diabetes Care* 1997;20(1):32–5.
- [16] Kurita A, Mochio S, Isogai Y. Changes in auditory P300 event-related potentials and brainstem evoked potentials in diabetes mellitus. *Acta Neurol Scand* 1995;92(4):319–23.
- [17] Papo D, Douiri A, Bouchet F, Bourzeix JC, Caverni JP, Baudonnière PM. Time–frequency intracranial source localization of feedback-related EEG activity in hypothesis testing. *Cereb Cortex* 2007;17(6):1314–22.
- [18] Ally BA, Jones GE, Cole JA, Budson AE. The P300 component in patients with Alzheimer's disease and their biological children. *Biol Psychol* 2006;72(2):180–7.
- [19] Struber D, Polich J. P300 and slow wave from oddball and single-stimulus visual tasks: inter-stimulus interval effects. *Int J Psychophysiol* 2002;45(3):187–96.
- [20] Woods DL, Courchesne E. The recovery functions of auditory event-related potentials during split-second discriminations. *Electroencephalogr Clin Neurophysiol* 1986;65(4):304–15.
- [21] Gonsalvez CJ, Polich J. P300 amplitude is determined by target-to-target interval. *Psychophysiology* 2002;39(3):388–96.
- [22] Polich J. Probability and inter-stimulus interval effects on the P300 from auditory stimuli. *Int J Psychophysiol* 1990;10(2):163–70.
- [23] Wronka E, Kaiser J, Coenen AML. The auditory P3 from passive and active three-stimulus oddball paradigm. *Acta Neurobiol Exp (Wars)* 2008;68(3):362–72.
- [24] Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care* 1997;20(3):438–45.
- [25] Vermeer SE, den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. *Stroke* 2003;34(2):392–6.
- [26] Brands AMA, Kessels RPC, de Haan EHF, Kappelle LJ, Biessels GJ. Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood-glucose levels. *Eur J Pharmacol* 2004;490(1–3):159–68.
- [27] Biessels GJ. Cerebral complications of diabetes: clinical findings and pathogenetic mechanisms. *Neth J Med* 1999;54(2):35–45.
- [28] den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, et al.. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003;46(12):1604–10.
- [29] Lee ZSK, Chan JCN, Yeung VTE, Chow CC, Lau MSW, Ko GTC, et al.. Plasma insulin, growth hormone, cortisol, and central obesity among young Chinese type 2 diabetic patients. *Diabetes Care* 1999;22(9):1450–7.
- [30] Hassing LB, Hofer SM, Nilsson SE, Berg S, Pedersen NL, McClearn G, et al.. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing* 2004;33(4):355–61.
- [31] Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, et al.. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham study. *Diabetes Care* 1997;20(9):1388–95.
- [32] Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* 1998;31(3):780–6.